Vismodegib for recurrent locally destructive basal cell carcinoma in a renal transplant patient

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Vismodegib for Recurrent Locally Destructive Basal Cell Carcinoma in a Renal Transplant Patient

Running head: Vismodegib in a transplant patient

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Solid organ transplant patients are at an increased risk of developing cutaneous malignancies owing to long-lasting immunosuppression. The strongest increase in incidence (35-fold) has been reported for cutaneous squamous cell carcinoma[1]. Basal cell carcinoma (BCC) may occur even more frequently, especially during the first years after transplantation[2]. The hedgehog-inhibitor vismodegib has been safely used for the treatment of locally advanced or metastatic BCC in immunocompetent patients since 2012 [3]. The experience regarding efficacy and safety of vismodegib use in organ transplant patients is limited.[4, 5]

We report a 72-year-old male caucasian patient with a history of renal transplantation who had been first diagnosed with a BCC of the nose in 1993 and subsequently underwent numerous surgical and radiotherapeutic interventions for his recurring tumour. Last in May 2016, a left-sided maxillectomy and partial resection of the zygomatic bone with defect closure via a scapula/latissimus dorsi-graft had been performed, but also this extensive intervention only yielded a R1-situation with infiltration of the orbital floor. As the patient refused orbital exenteration and another course of radiotherapy was infeasible with regard to pre-treatment dose of 60 Gray, the responsible interdisciplinary tumour board decided to offer vismodegib treatment. Postoperative imaging could not delineate distinct tumour remnants, yielding an adjuvant treatment situation. Routinely, the patient was on 5 mg of prednisone once and 0.5 mg of everolimus twice daily for immunosuppression. Since a search of the literature did not reveal any results on the concurrent use of everolimus and vismodegib, we excluded potentially harmful drug interactions with the drug manufacturer and our pharmacological department. Thereafter, treatment was initiated with the standard dose of vismodegib (150 mg once daily) in June 2016.

Initially, it was well tolerated and the first MRT-scan after 3 months revealed no signs of disease recurrence **(Fig. 1)**. Regular laboratory tests (complete blood count, renal and liver function parameters) did not indicate any drug interactions. Subsequently, the patient developed increasing dysgeusia as well as alopecia of the scalp and eyebrows, both well-known side effects of vismodegib[6] **(Fig. 2)**. After another unchanged MRT-scan in December 2016, we offered the patient an intermittent dosing-schedule of vismodegib to decrease side effects and improve quality of life. The patient consented to a 12-weeks-on/8-weeks-off schedule, according to arm A of the MIKIE study [7]. As of April 2017, the patient has completed his first drug holiday and regained sense of taste.

To our knowledge, we report the first case of concurrent use of vismodegib with mTOR-inhibitors in a transplant patient. Due to exclusion of transplant patients from clinical trials, data on the use of vismodegib post-transplantation are scarce. Also, locally advanced or metastasizing BCC may be less frequent in this patient population, owing to regular dermatological follow-up. Yet, local recurrence and invasion of BCC can occur despite continuous surveillance, eventually resulting in an indication for systemic therapy. Due to the aggressive course that BCC can take in immunosuppressed patients, adjuvant vismodegib treatment in a high-risk R1-situation as described seems reasonable.

Significant side effects occur in the majority of vismodegib patients, resulting in treatment discontinuation in almost 30% of patients [8]. Hence, intermittent dosing schedules of vismodegib have been recently investigated and may especially be feasible in transplant patients requiring long-term treatment for recurrent invasive BCC [7].

Concerning the combination of vismodegib with everolimus, a potential synergistic effect of mTOR- and hedgehog pathway-inhibition due to crosstalk of these pathways is of particular interest and has been supposed in different types of cancer [9]. Also in BCC, a potential role of the mTOR pathway is conceivable, as the incidence of BCC in transplant patients is reduced when mTOR inhibitors are used first-line for immunosuppression [10].

In conclusion, the concomitant use of everolimus and vismodegib appears to be safe and efficacious in our patient. Together with other reports published, this should encourage the inclusion of organ transplant recipients - in particular those treated with mTOR-inhibitors - in future clinical trials with hedgehog pathway inhibitors.

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Figure 1: Clinical Picture

(a) Patient at first presentation at our hospital in June 2013 with a visible recurrence of the basal cell carcinoma (black arrow).

(b) Preoperative picture before left-sided maxillectomy and partial resection of the zygomatic bone in May 2016.

(c) Patient after six months of vismodegib treatment without signs of disease recurrence in December 2016. Increasing alopecia of scalp hair and eyebrows was attributed to vismodegib.

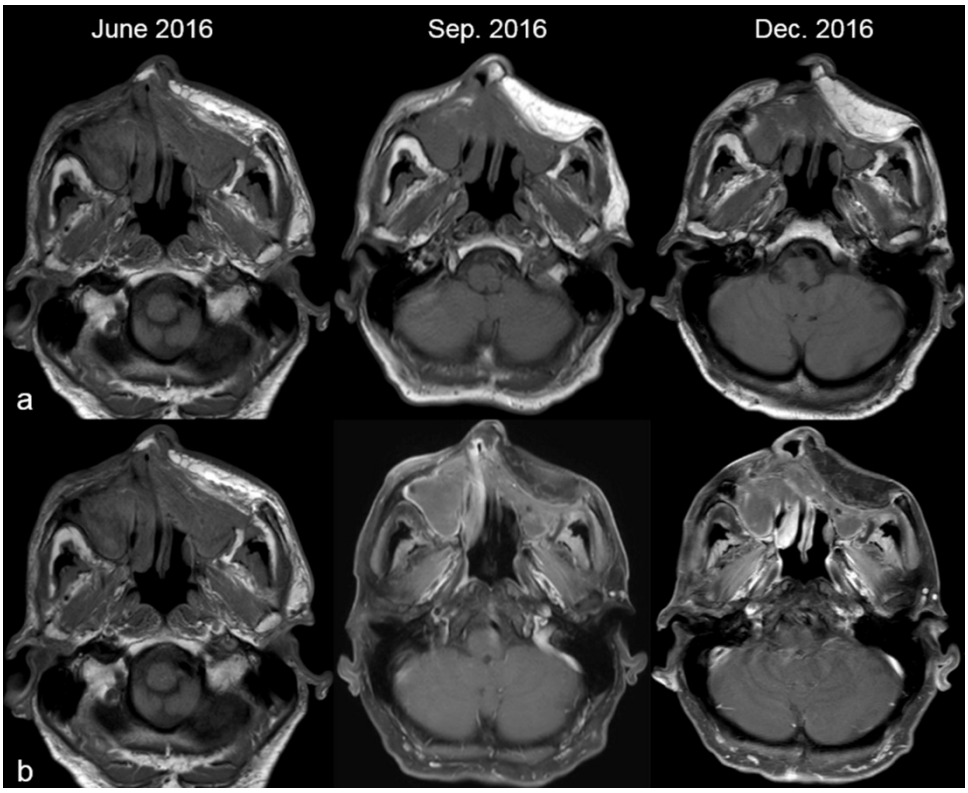

Figure 2: Magnetic resonance tomography (MRT) imaging

Sequential MRT scans showing diffuse postoperative oedematous changes in June 2016, five weeks after left-sided maxillectomy and scapula/latissimus dorsi-graft reconstruction. Subsequent MRTs during vismodegib treatment show regression of the postoperative fluid retention without signs of tumour recurrence. Physiologic fatty degeneration of the latissimus flap can be observed (a: T1-weighted sequence, b: T1-weighted, fat-suppressed sequence with Gadolinium contrast media).